Gastrointestinal Drugs Advisory Committee Meeting
February 23, 2010

DRAFT QUESTIONS FOR THE COMMITTEE

EFFICACY:

1. How should remission be defined in overt episodic hepatic encephalopathy (HE)?

2. In clinical trials conducted to support approval of products for **decreasing the risk** of developing of episodes of overt HE, what clinically meaningful endpoints should be evaluated (as primary and key secondary endpoints) and how should they be measured?

3. In clinical trials conducted to support approval of products developed for the **treatment** of HE, what clinically meaningful endpoints should be evaluated (as primary and key secondary endpoints) and how should they be measured?

4. Study RFHE3001 enrolled a patient population in which 2/3 of patients had a baseline Conn Score of 0 and 1/3 had a baseline Conn Score of 1. The study evaluated time to breakthrough HE event as defined by the increase in Conn Score of 2 or increase in Conn Score of 1 and increased asterixis grade by 1.

a. Does an increase in time to breakthrough HE event, so defined, constitute reduction in the risk of developing episodes of overt HE? (Vote)
b. Do increases in time to breakthrough HE events (as defined above) represent clinical benefit? (Vote) Please identify the specific benefit.

5. Do the clinical data in the Xifaxan application provide substantial evidence of efficacy for decreasing the risk of developing episodes of overt HE? (Vote)

a. If yes, which clinical data provided substantial evidence of efficacy? Specifically, which endpoints?
b. If no, what are the deficiencies in the clinical data that make you consider the evidence to be less than substantial?
c. Are there additional analyses or trials you feel should be conducted?

SAFETY:

6. Has the safety of Xifaxan at the proposed dose and duration been adequately assessed in cirrhotic patients with a history of HE? (Vote) If not, what additional analyses or trials are needed? In answering this question consider the adequacy of the submitted safety data addressing the following:

a. Child's Class C patients
b. Risk for development of resistant bacteria
c. Cardiac safety, i.e., potential for QT prolongation
d. Risk for *C. difficile* colitis

7. Is the safety of Xifaxan at the proposed dose and duration acceptable in cirrhotic patients with a history of HE? (Vote)

RISK/BENEFIT ASSESSMENT:
8. In light of the safety and efficacy data presented in this application, do you feel the risk benefit profile supports approval of Xifaxan for decreasing the risk of developing episodes of overt HE? (Vote)